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Reproductive Tissue Engineering

Balancing Ethical Pros and Cons of Stem Cell Derived Gametes

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Abstract—In this review we aim to provide an overview of the most important ethical pros and cons of stem cell derived gametes (SCD-gametes), as a contribution to the debate about reproductive tissue engineering. Derivation of gametes from stem cells holds promising applications both for research and for clinical use in assisted reproduction. We explore the ethical issues connected to gametes derived from embryonic stem cells (both patient specific and non-patient specific) as well as those related to gametes derived from induced pluripotent stem cells. The technology of SCD-gametes raises moral concerns of how reproductive autonomy relates to issues of embryo destruction, safety, access, and applications beyond clinical infertility.

Keywords—Artificial gametes, Assisted reproductive technologies, Embryo research, Gametogenesis, Infertility, Parenthood, Stem cells.

INTRODUCTION

In recent years, several research groups have conducted investigations aimed at the derivation of gametes from stem cells. This possibility is expected to greatly benefit basic and clinical research, especially in the field of assisted reproductive technology (ART) and stem cell research. Besides applications in the research setting, the great promise of stem cell derived gametes (SCD-gametes) resides in a future clinical application for reproductive purposes, enabling men and women who lack functional gametes to achieve (genetic) parenthood.[53]

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SCD-gametes can either be obtained from embryonic stem cells (ESC) or from somatic cells that are reprogrammed into so-called induced pluripotent stem cells (iPSCs). Other sources of SCD-gametes have received less (ethical) attention [e.g. germline stem cells (GSCs) or bone marrow stem cells]. Since our review aims to give an overview of the most important ethical pros and cons of SCD-gametes found in the literature, we will focus on SCD-gametes derived from human ESCs and iPSCs.

We will discuss the possible applications and respective concerns for both sources of SCD-gametes, as found in the literature. Despite the possible benefits of SCD-gametes, the possible use of this technology has also induced several ethical worries. We first discuss the ethical issues connected to the use of ESC-derived gametes, both for research and reproduction. The discussion of the latter application is divided in non-patient-specific and patient-specific derived gametes. We then discuss the ethical concerns raised by iPSC-derived gametes, followed by an overview of other ethical issues shared by both ESC-derived and iPSC-derived gametes.

GAMETE DERIVATION FROM EMBRYONIC STEM CELLS

Two sources of ESCs can be identified: embryos created by fertilisation or cloned embryos [created by somatic cell nuclear transfer (SCNT)].

In humans, the former source would imply the use of donated spare IVF embryos or embryos created from oocytes and sperm donated for this goal. Proof of principle is available in the mouse model, where embryos were created with ESC-derived sperm-like cells,

resulting in live offspring.[94] Also, in humans progress (albeit slower than in mice) has been made towards gamete derivation from ESCs.[28]

The second route to obtain ESC-derived gametes involves the cloning of an embryo by inserting the nucleus of a somatic cell into an enucleated oocyte. After culturing the embryo to the blastocyst stage, ESCs are obtained from its inner cell mass from which gametes can then be derived. These gametes would be patient-specific, and thus their use in infertility treatment would lead to a genetic link between the person whose somatic cell was used in the cloning procedure and the resulting child.

The use of ESCs, however, is controversial as it involves embryo destruction. It has been argued that even if one does not attribute an absolute moral status to embryos, embryos can still have moral value, because an embryo is "a developing form of life, and also a symbol of human existence" and therefore deserves some respect.[15,16,83] Many people consider it less disrespectful to use spare IVF embryos (which will be destroyed anyway), than to create and destroy embryos for (say) research. For this reason, it is possible that also in a reproductive context, some people will accept the creation of non-patient-specific SCD-gametes from spare IVF embryos, while disapproving the creation of patient-specific SCD-gametes from SCNT-embryos regardless of the fact that the latter will establish genetic parenthood while the former will not. Another possibility is that those who object to embryo creation in the research setting hold that establishing genetic parenthood outweighs the cons of creating and destroying embryos and therefore accept this reproductive usage.[16,52] It will thus be important to assess the benefits of both sources of ESC-derived gametes, for reproduction as well as for research. We will first consider the research benefit of SCD-gametes from spare embryos followed by their potential reproductive benefits. Next we explore the benefits of SCD-gametes derived from SCNT-embryos.

ESC-Derived Gametes in Research

In their 2004[87] and 2005[88] publications which started the ethical debate about SCD-gametes, Testa and Harris stated that the most immediate application will be for research purposes. In a more recent editorial, Eichenlaub-Ritter echoed this opinion.[22] Most research purposes which might benefit from the advent of SCD-gametes would not necessarily require that the gametes be patient-specific, and so for these purposes gametes derived from spare IVF embryos could be used.

To date, research depending on a supply of gametes has not only been hindered by ethical and legal objections, but also by practical hurdles, especially for obtaining oocytes.[56,88] Oocyte donation is a burdensome procedure with a risk of complications due to the ovarian stimulation and oocyte retrieval. Among the risks are the chance of developing ovarian hyperstimulation syndrome, possible infections, bleeding and (uncertain) long-term health effects such as an increased risk of cancer.[43] Remunerations for oocyte donors to compensate for their time investment, discomfort and risks in the hope of increasing the supply gives rise to additional ethical concerns regarding the commodification of human body material, undue inducement, exploitation, and fears for the emergence of an "egg donor underclass".[49,56] The issues of possible health risks and exploitation of healthy oocyte donors could be countered by formulating guidelines based on existing practices in the field of research involving healthy research subjects.[49] Commentators have stated that *in vitro* gamete derivation could not only sidestep the ethical concerns linked to oocyte donation, but could also offer a solution for the shortage of donor eggs.[38,44,49,56]

The research purposes which may thus be facilitated are manifold: It could promote the scientific advancements of SCNT, and thus serve stem cell research, as well as a better understanding of certain diseases.[87,88] A large gamete pool could allow to test hypotheses about gene-disorder relationships, and would facilitate assessments of environmental influences on the development of diseases, as well as investigation of how disorders are inherited.[46,82] It could generally facilitate research into gametogenesis, associated mechanisms underlying infertility, the general understanding of human fertilisation and developmental biology, the study of X-chromosome inactivation, imprinting, and the formation of germ-cell tumours in particular.[37,38,44,56,79] The gametes could also serve as a training resource for medical personnel, e.g. to learn the technique of intracytoplasmic sperm injection (ICSI).[44]

Those research applications involving the destruction of embryos created from gametes derived from spare embryos will likely be opposed by those who object to the creation of embryos for research purposes and will only be permitted in a limited number of countries. Lippman and Newman, however, referred to embryos created from SCD-gametes as "assemblages" suggesting that they would merit less moral respect.[41] Their argument seems to be that these embryos would not have any instrumental and/or emotional value attributed to them by their progenitors. However, their 'unnaturalness'[88,89] does not diminish their potentiality as 'developing forms of human life'[83] (unless it is argued that these embryos have a lower chance of survival). In sum, the main ethical issue here points back

to the question about the moral acceptability of instrumental usage of embryos.

ESC-Derived Gametes in Reproduction

The research into the generation of SCD-gametes is primarily motivated by reference to their potential reproductive use. Especially the goal of establishing genetic parenthood *via* SCD-gametes is regarded as an important objective (for researchers explicitly citing this objective see e.g. Refs. 3,21 and 27. See Ref. 29 for an overview of stakeholder groups' reporting). To achieve this, patient-specific gametes will have to be created, which requires gamete derivation *via* either SCNT or iPSCs (see below). Although non-patient-specific ESC-derived gametes are mainly thought to benefit basic research (as discussed above), they may also be useful for reproductive ends, namely as donor gametes.

Non-patient-Specific ESC-Derived Gametes in Reproduction

Derivation of gametes from embryos created by fertilisation is possibly closer to clinical application than the creation of 'tailor made' gametes *via* SCNT or iPSCs. A promising step has been made by Zhou *et al.* who derived functional spermatids from mouse ESCs which conformed to the 'gold standards' of *in vitro*-derived germ cells.[94] If this technique proves to be applicable in humans, then the creation of a supply of gametes derived from spare IVF embryos could be used for reproductive ends. These gametes could be used to establish a pool of gametes for 'third party' assisted reproduction. Importantly, here the donor gametes do not stem from a consenting adult, but from a surplus IVF embryo which was donated by consenting adults. Like in 'normal' donor assisted reproduction, at least one of the parents will not be genetically linked to the resulting child. The scenario of donor assisted reproduction by means of SCD-gametes may, however, have some advantages over 'normal' donor conception.

From the perspective of the future parents, donor assisted reproduction by means of non-patient-specific ESC-derived gametes might be an attractive possibility as it would eliminate the threat of a parental claim by the donor.[26] In case of traditional donor assisted reproduction some parents fear that the donor's genetic link with the child would give him the status of a "real parent", and that this link would be sufficient for him to claim parenthood and the associated rights and duties.[65] Also when anonymous donation is used, couples tend to minimise the donor's contribution to "a little seed"[93] to reduce the possible threat to their relationship with the child. When ESC-derived gametes are used, however, there would be no third party alive who could count as a genetic parent (as the embryo is destroyed in the process of gamete derivation). Consequently, there could be no fears for conflicts about parental rights or duties (unless such rights are also accorded to genetic grandparents, here: the donors of the embryo).

It has been argued that also from the perspective of the future offspring this would be a good thing. Sparrow, for instance, speculated that it might be better for a child to be born without genetic parents than to be conceived using donor gametes, because the latter case might induce feelings of being abandoned by one's genetic parents (which Sparrow deems even worse).[81] However, it has been argued that such a practice would be psychologically harmful, and therefore unacceptable for the future offspring.[42,44,51,56,92] Watt, for instance, has stated that as the genetic parent/gamete donor never existed as a person and the resulting child could therefore not possibly know this genetic parent, the child might feel "cast adrift on the world".[92] Given the current focus on the so-called right to know one's genetic origin (which also functions as an argument to abolish donor anonymity), this application is being labelled by some as immoral.[51,67]

While such considerations have some bearing on the ethics of this practice, others have emphasised that rationalisations about the psychological impact of being born without genetic parents are necessarily speculative, and should not be exaggerated.[51,81,82] It has been argued that similar concerns from the past (e.g. concerning IVF and donor conception) have not been confirmed.[51] Probably much will also depend on how these issues will be framed. Master has also argued that there is no specific psychological harm to be expected for children born from ESC-derived gametes, because such a treatment is just as "artificial" as other ARTs (where the psychological wellbeing is similar to that of naturally conceived children).[44] He focusses however on the 'artificiality' of the treatment and does not mention the possible psychological harm of not knowing one's genetic parent.

Yet, another issue related to the embryo's statute as a gamete donor has been raised. According to Watt it is morally wrong to force embryos into parenthood, because embryos too have a stake in their future, and therefore it is morally wrong to harvest gametes from embryos without their consent.[92] Similarly, according to an Ethics Committee statement of the Human Fertilisation and Embryology Authority "it must be conceded that the gametes are not the gametes of a person who, in any possible world, would be capable of giving their consent to use".[34] The problem with this argument is that 'informed consent' is a principle that

is based on respect for a person's autonomy, while an embryo is not a person, let alone an autonomous one. There is only one conceivable situation in which the lack of an informed consent of the embryo would be a valid concern: if the ESCs would be acquired through a biopsy and the biopsied embryo would be transferred to the womb, leading to a person in the future. As reproductive autonomy involves the right to decide whether to have children, when, with whom, etc., one could say that this would violate this future person's reproductive autonomy: (s)he would be a genetic parent even before (s)he could decide whether (s)he wants this or not. Although technically feasible,[8] this scenario is rather theoretical.

If informed consent cannot be provided by the embryo, should it then be obtained from the donors of the embryo? One might say that this resembles requiring consent from previous generations for reproductive endeavours. As the donors of the embryo would be genetic grandparents, and as grandparents cannot donate their children's gametes for reproduction, it can be argued that an explicit informed consent should not be sought from the original donors. First, this analogy compares an embryo to a child, and therefore seems to falsely presuppose that embryos are children. Second, it does not as such concern the tissue of the donors of the embryo, but rather gametes that were produced from ESCs produced from the embryo that was created from their tissue.[51] However, without entering into the difficult debate about the extent to which people own their tissue,[77] a pragmatic approach can be advocated that incorporates informed consent. A modest claim can be made that in recognition of a donor's gift for the benefit of therapy or research, his or her tissue should not be used for purposes that the donor perceives as morally objectionable. As gamete generation gives rise to moral concern (as shown in this review), informed consent needs to be sought from the embryo donors. Firm policies on this issue also help to maintain trust in research and counter speculations that the possibility to derive gametes from ESCs would prevent IVF patients from donating their spare embryos for stem cell research, as they might fear that rather than being used for research, they might be used to derive gametes for reproduction.[77,79] It has been shown that people's perception of science influences the willingness to donate spare embryos for research, which also suggests that proper information about scientific research with embryos could overrule the fear of improper use.[64]

Finally, if gametes derived from spare IVF embryos are ever to be used for reproduction, embryos will have to be created in order to preclinically assess their functionality and to evaluate whether or not these embryos show signs of abnormal development.[29,46,52] Here, contrary to the production of patient-specific ESC-derived gametes, embryo creation and destruction is not inherent to creating ESC-derived gametes, but it is morally required as a research step if the technology is to make it to the clinic. If this step is skipped, then these experiments will lead to the birth of children who will be exposed to unnecessary risks.[29,52]

Patient-Specific ESC-Derived Gametes in Reproduction

Contrary to reproductive use of non-patient-specific ESC-derived gametes, so-called 'tailor-made' gametes derived from SCNT-ESCs do hold the promise of establishing a genetic link between the parents-to-be and the future child. Because society highly values genetic ties, and many people regard genetic parenthood as an important life goal, the creation of patient-specific gametes from SCNT-ESCs holds an additional advantage.[29] Here, the ethical concerns of possible psychological effects on the offspring of being "orphaned at conception",[81] the issue of obtaining informed consent from an embryo, as well as safety issues also apply. It has been argued, however, that the value attached to genetic relatedness could, in fact, lessen the grip of these concerns.[56,87] The strength of such claims mainly relies on the assumptions that the end justifies the means, and that the means actually serve the end. However, in the literature, it has been questioned whether the importance of being genetically linked to one's children is sufficiently great to justify reproductive risk-taking and whether patient-specific SCD-gametes do indeed lead to genetic parenthood.

It will be critical to assess these assumptions, especially given the fact that the derivation of patient-specific gametes from SCNT-ESCs holds additional safety and other ethical concerns. Derivation of gametes from SCNT-ESCs not only inherently implies creation and destruction of human embryos,[36,52] the technique is also premised upon the availability of high quality oocytes and thus re-raises the ethical concerns connected to oocyte donation.[39] Above all, authors have pointed to the additional safety risks of this route, such as potentially harmful genetic and epigenetic mutations, not only affecting the health of the future child, but also that of future generations.[44]

The benefits of creating patient-specific SCNT-ESC-derived gametes over using naturally produced donor gametes and over non-patient-specific ESC-derived gametes should thus outweigh all these concerns. However, these benefits may be more limited than portrayed. For example, it is generally assumed that patient-specific SNCT-ESC-derived gametes will establish genetic parenthood.[28,36,88] It is doubtful whether this is the case. Above we already referred to the embryo from which the gametes are derived as the 'genetic parent'.

Similarly here, the cloned embryo from which the gametes are derived, counts, in fact, as an extra generation.[50] Although the person whose somatic cell is used to create the cloned embryo would share 50% of his/her DNA with this person, the case can be made that the resulting child is his or her twin's child, even though that twin is not "more than a ball of 150 cells".[50] It would therefore seem that patient-specific SCNT-ESC-derived gametes do not necessarily meet the promise of establishing genetic parenthood. For one thing, Mertes has argued that much will depend on how 'genetic parenthood' is understood, as this concept is not fixed once and for all, but is rather subject to scientific and societal changes.[48] For example, if we want to maintain the idea that people are not the genetic parents of their identical twin's children, it will be difficult to argue that gametes derived from a cloned embryo lead to genetic parenthood, unless genetic parenthood is not defined based on a fixed set of necessary characteristics, but rather on some kind of ranking mechanism (e.g. 'if somebody exists that contributed 50% of DNA and has a direct physical link to the child then (s)he is the genetic parent, if nobody has a direct physical link, then contributing 50% of DNA is a sufficient condition for being a genetic parent'). On the other hand, genetic parenthood can also be accorded to anyone who contributed any small piece of DNA. For example, the highly contested characterisation of children born after mitochondrial replacement therapy as 'three parent children', implies that even minor genetic contributions (0.15% of the total DNA in this case) lead to (a degree of) genetic parenthood.[2,57]

This leaves us with the second question: is the end of genetic relatedness important enough to justify the means (creating patient-specific gametes *in vitro*) and overcome the related ethical concerns? Several authors have asked about the moral significance of the wish to have a genetically related child, and whether this is proportionate to the potentially high health risks, especially to the future offspring.[5,9,17,48,62,77,80] It is, however, difficult to operationalise the principle of proportionality. Further ethical reflection will be needed to assess the moral significance of genetic relatedness in parent–child relationships and how this may or may not affect people's reproductive autonomy.

Such discussions about the welfare of the child are further complicated by the so-called non-identity argument (NIA).[11,40,59,61] Quite contrary to most people's intuition, it is argued that a child who is brought into existence by a risky technique (such as SCD-gamete technology) cannot be harmed by the use of this technology, because without the use of it, (s)he would never have existed at all. That is: unless (s)he has a life not worth living, meaning that her level of welfare is so low that it is worse than non-existence. Contrary to the conclusion of the NIA, one could use impersonal considerations to argue that, albeit nobody is personally made worse off, it is nevertheless morally wrong to use such risky techniques.[40] From an impersonal point of view it would be morally worse if children born *via* risky techniques had a lower quality of life (although their life is worth living), than children born *via* less risky techniques. To use Parfit's words: "If in either of two possible outcomes the same number of people would ever live, it will be worse if those who live (…) have a lower quality of life, than those who would have lived".[60] Savulescu and Kahane, on the other hand, use the intuitive response to the NIA (that it is wrong to use such risky techniques) as an argument to defend their view about the principle of procreative beneficence (PPB).[69] PPB holds that when a couple plans to have a child, they have significant moral reasons to select, of the possible children they could have, the child who is most likely to experience the greatest wellbeing.[4,69] In this sense, if a couple considers the options of either conceiving a child with donor gametes or with SCD gametes at a moment when the health prospects of offspring from SCD gametes are considerably lower, they have moral reasons to select donor conception.

It is a contentious point where the bar should be set for this level of welfare.[61,76] Several guidelines have nevertheless been established.[33,62] The standard adopted by the European Society of Human Reproduction and Embryology is that medical professionals should refrain from offering the technique in case of "a high risk of serious harm to the future child", according to the presently known risk factors.[62] The rationale behind this threshold is that a 'reasonable welfare level' should be guaranteed to the future child, although it is difficult to give a clear conception of what this amounts to.[61,62] Moreover, it is not unique to the reproductive use of SCD-gametes that the value of genetic relatedness is weighed against the risks to the future offspring.[7,30,63] It should be further investigated whether for SCD-gametes the risks to the offspring are sufficient to prohibit its use.

Although genetic relatedness is highly valued in parent–child relationships, establishing it *via* patient-specific ESC-derived gametes raises practical and ethical concerns. These become especially contentious due to the fact that it might not lead to 'full' genetic parenthood. Most of these issues could be overcome by a possible future introduction of iPSC-derived gametes.

GAMETE DERIVATION FROM NON-EMBRYONIC STEM CELLS

Regarding non-embryonic SCD-gametes, most of the attention has gone to gametogenesis from iPSCs.

iPSCs can be obtained by genetically reprogramming adult somatic cells, which yields pluripotent cells with capacities similar to ESCs.[43,86] While it has proven to be difficult to generate human oocytes from iPSCs, sperm-like cells have already been derived from iPSCs in humans.[21,28,31]

Other non-embryonic sources of SCD-gametes that are being explored seem less promising than the iPSC-route. For instance, SCD-gametes could be derived from GSCs, but for infertile people whose gonads do not contain GSCs, this is not a real treatment option.[28,53] Alternatively, bone marrow stem cells have also been suggested, but their potential to differentiate into gametes is still under discussion.[3]

Mertes and Pennings introduced the issue of iPSC-derived gametes to the ethical debate and concluded that given the scientific state-of-the-art, deriving gametes from iPSCs would be less controversial than deriving them from ESCs, provided that the safety concerns would not be greater for iPSCs.[52] Importantly, gamete derivation from iPSCs, if obtained under proper informed consent, poses fewer ethical problems than gamete derivation from cloned embryos.[36] No donor oocytes, nor embryos are needed and thus issues of egg cell harvesting, and controversies surrounding embryo destruction are circumvented.[75] Therefore, the iPSC route has been welcomed as "an ethical alternative".[54] Since there is no embryo from which the gametes are derived, there is also no problem of the embryo being the genetic parent, rather than the donor of the somatic cell. It will be the consenting future parent whose somatic cell will be reprogrammed to become stem cells, which will subsequently be differentiated into germ cells.

According to Smajdor and Cutas, however, the possibility to "create gametes from stray skin cells" invokes questions about "unwitting parenthood" which leads to associated issues about the practice of ascribing parental rights and obligations on the basis of genetic connections.[77] This possibility to create gametes from the nucleus of a somatic cell, has also led Sawai to warn that iPSC-technology might call for a reconceptualization of the ethical value of iPSCs (this has also been hinted at by de Wert[13]).[70] That is, if human embryos are accorded moral value because of their potential to develop into a person, the iPSCs technology might engender similar attitudes towards iPSCs since these too are capable of developing into mature human beings. Sawai adds, however, that this argument is premised on the existence of a technology for the cells to develop into human embryos or foetuses, and that there is the intention to use the technology in this way.[70] But even if these criteria are met, this argument can be disarmed by pointing to the fact that a somatic cell as such cannot become a person, and that even after cell reprogramming by induced pluripotency, the iPSCs still have to be differentiated into gametes.[25] Then again, a gamete by itself does not have the potential to become an embryo, let alone an adult.[25,42] Thus, the potentiality argument does not hold for gametes, let alone iPSCs.

The question whether iPSC-derived gametes could really serve as 'an ethical alternative' for SCNT depends on the efficacy and safety of both these routes to create patient-specific gametes for reproduction. To be sure, the production of iPSC-derived gametes is still in its infancy and many hurdles concerning the safety of the process still remain. To date, there is no consensus about reprogramming and validation methods to obtain iPSCs,[74] and (as with SCNT) there are serious concerns about (epi)genetic alterations in iPSCs, increased risks for accumulation of chromosomal aneuploidies, and possible tumorigenicity.[36,53,54] Continuing research is needed to allow advanced comparisons of the (epi)genetic and transcriptomic impact of the two routes (SCNT versus iPSC).[85] Moreover, although recently a promising step has been made in mice,[31] some crucial steps will have to be made to make the leap to humans (as, e.g., human gametogenesis is different from mice gametogenesis). Finally, here too human embryos will have to be created in the research phase to ensure the safety of the technique.

OTHER ETHICAL ISSUES

The ethical issues discussed so far are not the only concerns about a future reproductive use of SCD-gametes. Additional ethical issues can be found in the literature which are not specific to iPSC-derived gametes, but which equally apply to SCNT-ESC-derived gametes. Assuring the safety of iPSC-derived gametes is therefore not an a priori sufficient condition to accept their reproductive use.

The advent of SCD-gametes is mainly welcomed because of their potential to treat 'infertility'. As such, the technology could be used in the future to treat infertility due to damaged gonads as a result of injury or disease.[84] It could, for instance, enable women with premature ovarian insufficiency and men with non-obstructive azoospermia to become genetic parents.[28] Also survivors of malignancies who are unable to reproduce due to, for instance, cancer treatments might also be able to have genetically related children by means of SCD-gametes.[3,36] Cases such as these are—apart from the ethical issues discussed above—relatively uncontroversial.[29] Other applications, however, are more controversial, such as 'treatment' for postmenopausal and premenarche women,

same-sex reproduction, solo-reproduction and multiplex parenting.[10,20,26,28,46,55,59,79,81,84,87,88]

Much of the opposition against these latter applications has been ascribed to intuitive responses often referred to as the 'yuck factor'.[51] This is rather common to new innovations, and is certainly not new to interventions on human reproduction.[9,71] Moreover, Hendriks *et al.* found that also for some couples diagnosed with non-obstructive azoospermia, treatment with SCD-gametes would feel 'unnatural', although they would still opt for such treatment.[30] In general, judging that something is uncommon or disgusting is not sufficient to morally condemn it.

Another argument that has been advanced against these more 'controversial' applications is that they do not 'cure' or repair flaws in the natural state of things and that medicine should stick to treatment, rather than innovation or enhancement. E.g. the treatment of premature ovarian insufficiency and non-obstructive azoospermia 'fixes' some deficiency so that 'normal' functioning can be restored and could therefore be accepted. On the other hand, for postmenopausal women the inability to naturally reproduce is 'normal' and so it is not medicine's task to enable it. This argument, however, goes wrong by making the leap from is to ought, since the natural as such is morally neutral.[10,51,88] This appeal to nature often merges with the objection that these more 'controversial' applications do not really treat 'infertility'. 'Infertility', however, is a contested concept. Because definitional criteria and criteria of eligibility for treatment are intertwined, it is difficult to pin down what 'infertility' means.[78] Intuitively, it might be held that 'infertility' denotes a physiological incapacity to have genetic offspring without medical help, and that eligibility for treatment is, implicitly or explicitly, premised upon the presence of a reproductive pathology.[78] Smajdor and Cutas, however, argue that ARTs actually treat people's reproductive aspirations "regardless of whether the patient is suffering from a reproductive pathology" (popular media[90] reported that the World Health Organisation is moving towards such concept of infertility).[78] Consequently, so they argue, any coherent clinical reasons to provide treatment to some and deny it to others, evaporate. Thus, from the moment that a new technology would become available which would enable these groups to have a genetically related child, these people would also have a claim to access this treatment. This explicates the point that the development of the SCD-gamete technology may engender new needs, which might further increase the importance of genetic ties in parent–child relationships.[78]

It also calls for a more elaborate exploration of access and justice concerns regarding the use of the technology.[6,9,26,29,78] The SCD-gamete technology will likely be expensive, at least in the beginning. If in the first years after its introduction enough people are willing to pay for it, Greely argues that this could get the attention of "drug and biotech companies, and venture capitalists".[26] Eventually, an increase in efficiency will probably lead to a reduction of costs. But this does not mean that it will become affordable for everyone who wants to use the technology. It might therefore be argued that access should be covered by health insurance. In a context of scarcity, this would raise serious problems of resource allocation if everyone who could benefit from the technology would be eligible for reimbursement. A similar argument could be made against the investment of public resources into developing the SCD-gamete technology. Rulli argued (in the context of mitochondrial replacement techniques) that the desire to have genetically related children lacks the social value to justify investment in developing such techniques, given finite resources and the opportunity costs of investing in more urgent interventions.[68] Although it could thus be argued that investment of public resources in the development of SCD-gamete technology to attain genetic relatedness would be unethical, one must also weigh the social value of the other (scientific) benefits of the technology.

Finally, each of these applications have led to separate discussions. We will explore the most common arguments in turn.

Postmenopausal Women

One important argument in favour of the reproductive use of SCD-gametes by postmenopausal women builds on the equality argument since men can have children up to a high age.[18,23,84]

A contra-argument against postmenopausal pregnancies is that the resulting children would be less likely to have a long-term relationship with their mothers. Correspondingly, these children will more likely suffer the loss of one of their parents before reaching adulthood.[10,23,84] Although this event may be harmful to the child, a reduced life expectancy is not a sufficient condition to exclude someone from parenthood.[10]

Another contra-argument is that these women's advanced age might make the parental project too demanding (Suter similarly sees the early age and 'unreadiness' of premenarche girls as the main reason why these girls should be denied use of SCD-gametes, since this would negatively affect the interests of both mother and child[84]). According to Cutas and Smajdor, however, "frailty" is not exclusive to women of advanced age, and excluding them from parenthood on these grounds would therefore be discriminatory.[10]

Rather, it has been argued that each woman's particular situation should be evaluated individually, equally taking the health and coping abilities both of herself and her partner (if present) into consideration.[10,51]

There might, however, be an additional concern that the age of the somatic cell from which the egg cell is derived might influence its quality.[51] These concerns should again be weighed against the value of reproductive autonomy and of genetic parenthood.

Same-Sex Couples

The reproductive use of SCD-gametes for same-sex couples is also grounded in an equality argument.[14] Having a genetically related child is an important life goal for many heterosexual couples, and there is no a priori reason why this should be any different for same-sex couples. Same-sex couples, however, normally lack the options to obtain shared genetic parenthood and therefore often resort to 'symbolic gestures'.[19,55] Alternatively, Baylis suggested that non-therapeutic use of mitochondrial replacement technology would allow lesbian couples to parent a child who is genetically related to both parents: one mother providing the nuclear DNA, the other providing the mitochondrial DNA.[2] SCD-gamete technology, however, promises a more substantial genetic relatedness, both for lesbian and gay couples.

If clinical use of SCD-gametes would ever become available, then 'being gay or lesbian' is no valid argument to exclude same-sex couples from using the technology. Several authors have stated that fears about the psychological welfare of children parented by same-sex couples are not exclusive to the debate about reproductive use of SCD-gametes, and are, furthermore, ungrounded.[1,14,20,51,55,84,88] Analogously, the claim that the children's psychological welfare might be harmed due to the 'strangeness' of the process *via* which they are conceived, is not an exclusive argument against same-sex reproduction by means of SCD-gametes, but equally applies to heterosexual couples using that technology.[44,88]

The one relevant aspect in which reproduction *via* SCD-gametes differs between same-sex couples and heterosexual couples, is that there is an additional concern about the feasibility of the technique. Same-sex reproduction by means of SCD-gametes is conditioned upon the ability to derive male germ cells from female stem cells or *vice versa*.[28,46,55,59,87,88] To date, little scientific progress has been made in this direction, which has been coined the "most challenged goal in the artificial gamete generation".[53] Especially the derivation of sperm from women is considered to be very difficult or maybe even "impossible".[32] In particular, this procedure raises important safety concerns connected to fears about faulty imprinting.[51,88] Overcoming the imprinting issue, moreover, will likely require genetic modification, which raises additional ethical issues about the acceptability of genetically modified offspring.[88]

There is, however, an alternative route for same-sex couples to have genetically related offspring by means of SCD-gametes. This alternative makes use of ESC-lines to derive gametes, but it avoids the safety issues connected to either iPSC or SCNT, as well as the problems of imprinting specific to reprogramming stem cells to germ lines of the opposite sex. If a gamete could be derived from an embryo obtained after combining one of the partner's gametes with a donor gamete, then this ESC-derived gamete can be combined with the other partner's complementary gamete in order to create a child which is genetically related to both partners, albeit not in the same degree. One partner would share 50% of the child's DNA, the other partner 25%, as would the donor. Because both this partner and the donor would share an equal amount of DNA with the child, this partner would not have to fear that his or her parental claim would be trumped by the parental claim of the donor, which might be deemed a great advantage by many same-sex couples who wish to have a child. Note that if two male partners would make use of this possibility, surrogacy would still be required.

This scenario might, however, give rise to a rather semantic discussion about whether 25% would be enough for the one partner to count as a genetic parent. Similar discussions have been raised in response to the 'traditional' route for same-sex couples to reproduce by means of SCD-gametes: Newson and Smajdor contemplated whether a man whose DNA is contained in the oocyte used to produce a child would be recognised as a 'biological' *mother*.[56] According to Murphy, discussions like these are not very rewarding as long as they attempt to "retrofit all parents into mutually exclusive categories of mother and father".[55] Instead, he goes on to argue, these discussions should be reoriented towards the "more searching question, (…) whether these categories offer an adequate vocabulary for expressing the relationships progenitors can have with their progeny".[55]

Solo Reproduction

Cutas and Smajdor point at how solo reproduction by means of SCD-gametes may create such new types of genetic relations.[11] The possibility to combine a 'natural' gamete and a derived gamete from the same individual into an embryo has been pointed out quite early in the ethical debate.[56] However, as Carbone has stated, it is unlikely that solo reproduction by means of

SCD-gametes will occur, due to absent public demand.[6] Also Palacios-González *et al.* doubt whether this kind of solo reproduction is a value that should be protected.[59]

One of the ethical issues that has been raised in the literature in relation to such a prospect is the fact that such a person would be "mother and father in one".[11] Cutas and Smajdor have argued that this is not a priori problematic in terms of parental genders, since the concepts of motherhood and fatherhood are not fixed.[11] Suter contends that this problem of conceptualisation in itself is not sufficient to condemn solo reproduction, but that it, in combination with health risks to the offspring (see below) and concerns about depriving children of a genetic parent, does "raise serious red flags".[84]

Regarding the latter issue, Cutas and Smajdor agree that solo reproduction limits the offspring's possibility to enrich one's identity by not having knowledge of two branches of genetic relatives, although they also outline possible advantages such as a stronger bond with the single genetic parent.[11] Yet, again concerns about possible psychological impacts on the offspring are necessarily speculative.[81,84]

Risks of disease and disability associated with consanguinity are however not speculative.[52,84] The question whether the extent to which these risks could be reduced in the future would be 'enough', re-raises the issue of proportionality discussed above.[11,84] Note that the argument that this would not be in the best interest of the child would also be vulnerable to the non-identity argument (as the only other option is for that child not to exist, while it is in the child's interests to exist as long as her life is on the whole worth living).[59]

Multiplex Parenting

While the rationale behind solo reproduction seems to be the wish to avoid involvement of others in the reproductive process,[84] multiplex parenting would, instead, facilitate a "much more substantive sharing of genetic kinship".[59] Palacios-González *et al.* introduced the possibility of multiple persons—say four—parenting a child born from SCD-gametes, who is genetically related to all of them.[59] This scenario would first require the creation of two embryos from either couple, from which ESC-lines would then be derived to differentiate into gametes. These gametes could finally be used to create an embryo which is genetically related to all four of its "grandparents".[59] Since the gametes would be derived from embryos created through fertilisation, this scenario would be safer than solo reproduction or scenarios which require SCNT or derivation of gametes from iPSCs.

Although Palacios-González *et al.*[59] believe that this possibility would expand reproductive autonomy by liberating parenting roles from the constraints of biological generations *in vivo*, the main question is whether there would be any demand for such an application.[6] Palacios-González *et al.*[59] mention the specific situation of polyamorous relationships, but as Suter[84] commented, few people would probably wish to parent a child with more than one person. It could be argued that if multiple parents feel responsible for the child (which in fact is not premised upon this use of SCD-gametes) the child might be better off. At the same time, given that two parents who are raising a child often conflict about parenting approaches, there is an even higher chance of such conflict if more parents would be involved in the social parenting project. Even if four-way genetic parenting would be workable, then one might at least worry that in case of more elaborate networks it would be next to impossible to maintain between each parent and the child the kind of intimate relationship that is central to social parenting.[84] In such a context, Suter argues, the intimacy and the social connections between the child and each of the parents would diminish.[84]

Germline Gene Modification

Sparrow argued that the creation of various generations of embryos from SCD-gametes could be a possible route for human genetic enhancement, a practice which he called "*in vitro* eugenics".[45,82]

As talk about eugenics often raises many red flags,[24] commentators have soothed worries about *in vitro* eugenics by arguing that few people would be willing to sacrifice strong genetic ties with their offspring in order to have genetically enhanced children.[47,73] That is, *in vitro* eugenics would seriously 'dilute' the genetic link between 'parent' and child, which is highly valued by many people.[47,73] Moreover, in order to assure the success of this technique and the reliability of the data derived from it, the human embryos should be brought to term, which, according to da Fonseca *et al.*, would be "far from being ethically and socially acceptable."[12]

Alternatively, SCD-gamete technology could be used to produce many embryos from which the embryo with the 'best' genetic traits could be selected.[4,26,37,46] There are, however, newer, cheaper and more efficient genome editing technologies on the horizon such as the CRISPR/Cas9 systems.[45,91] As embryos and gametes are less accessible for gene editing than stem cells, it has been argued that it would be easier first to edit the iPSCs or SCNT-ESCs derived from the patient's somatic cell *via* CRISPR/Cas9, and then to differentiate these pluripotent stem cells into gametes.[91] The ethical issues raised by human germline modification are,

however, not specific to the technology of SCD-gametes.[52]

Human–Non-human Chimeras

A final issue for further analysis and debate concerns an alternative method of differentiating pluripotent stem cells as recently proposed by Palacios-González.[58] This proposal links in with recent efforts (currently at the animal research stage) that may eventually lead to creating personalized human transplantation organs by letting them grow from patient-derived iPSCs injected in an animal embryo in which the capacity to develop the relevant organ has been genetically disabled.[35,66,72] The idea is that this would lead to the birth of a cross-species (human–animal) chimera from which a fully human organ could then be harvested. As these organs would from conception grow in a natural environment designed for their development, this is thought to be a more promising route than creating organs *in vitro*. Palacios-González has suggested that the same technology may also be used as a way to create human gametes both for research and reproduction, while discussing some of the ethical issues arising, including the proportionality of this method in the light of the precise degree of infringing upon the interests of chimeric animals.[58] Clearly, subsidiarity considerations are relevant here as well.[72] If functional human SCD-gametes can be created *in vitro*, there is no need for the morally more challenging chimera route.

CONCLUSION

SCD-gamete technology holds promising benefits both for basic science applications and for clinical use in assisted reproduction. To date, it seems reasonable to say that use of SCD-gametes for research is nearest in time. For these purposes spare IVF embryos which were donated for science could be used. The derivation of gametes from existing ESC-lines is probably less complicated than producing SCNT-ESC derived gametes or iPSC-derived gametes. Although spare IVF embryos could be used to derive gametes, research into their functionality necessitates the creation (and subsequent destruction) of embryos, as would other possible applications. The main ethical issue here would thus come down to the question whether it is morally acceptable to create the necessary research embryos.

The same goes if ESC-derived gametes from spare embryos would be used for donor assisted reproduction. Only here there are additional concerns about informed consent, potential psychological harm to the offspring and, again probably the most poignant, the necessity to create and destroy embryos in order to test whether the technique is safe.

These issues also apply for the derivation of patient-specific SCNT-ESC-derived gametes. Some would a priori condemn this use of SCNT-ESC-derived gametes, since it inherently requires embryo creation and destruction. While it has been argued that here these concerns could be outweighed by the value of establishing a genetic link, reproductive use of SCNT-ESC--derived gametes would be unacceptable at this time because of the potentially high risk to the offspring.

Most of these problems would be overcome by the possibility to derive gametes from iPSCs. The main ethical issue connected to this route would again be the potentially high risk to the physical welfare of the resulting offspring (and possibly also that of following generations).

Note, however, that if one accepts the NIA, the arguments regarding risk and harm to the offspring only hold from the point of view of an impersonal account of morality, as the only other option for the offspring is not to exist.

Finally, even if these safety concerns can be remedied, there are still additional concerns about who would be allowed to benefit, and how access should be organised.

In short, the strongest arguments against the use of SCD-gametes at this time all point back to the prerequisite that the technology needs to be safe, especially if the controversy around embryo destruction can be avoided by the use of iPSCs.

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There are no relevant conflicts of interest.

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